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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,861	11/01/2001	Johan Ericson	21882-502	6942

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,861	ERICSON, JOHAN	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17,18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,17,18 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/20/05 has been acknowledged.

Claims 13-16 and 25-71 are canceled.
Claims 1-12 and 17-24 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Earlier applicant's elected Group I claims 1-24, wherein the elected subject matter is **stem cell differentiation**, Groucho co-repressor protein **Grg4** and Groucho interacting protein **Nkx2.2** in the reply filed on 01/13/05.

Claim Rejections - 35 USC § 112

Claims 1-12, 17-18 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the fate of differentiation of a chicken neural stem cell into a ventral neuron, by introducing into the neural stem cell nucleic acid encoding the Nkx2.2 gene which upon expression forms complexes with Grg4, does not reasonably provide enablement for a method of guiding the fate of differentiation of any other cell type by contacting the cell with any other Groucho-interacting proteins which forms complexes with any Groucho-corepressor proteins in-vitro or in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the same reasons of record as set forth in the office action mailed on 04/20/05.

Response to Arguments

The applicant arguments regarding enablement issue on pages 5-6 of response filed on 10/20/05 has been fully considered. The applicant argues that the specification as filed is enabled form guiding the fate of differentiation of a neuronal progenitor/stem cells into any kind of neuron by providing to the neuronal progenitor/stem cells any GIP that interacts with any Groucho-corepressor proteins in order to guide the fate of differentiation. In support the applicant cited Eberhard et al, 2000 and concluded there is sufficient evidence that Grg1, Grg2, Grg3 or Grg4 would have similar functions and that there is no reason to believe that Grgl, Grgz, Grg3 and Grg4 cannot be used in combination or interchangeably with one another. Regarding the use any GIP the applicant cited Pabst et al, 2000 and argues that NKx2.2 and Nkx2.9 share closely related structure, expression patterns, and dependence on Shh during early stages in embryogenesis. Citing Vallstedt et al., 2001, the applicant argues that NKx6.1 and Nkx6.2 exhibit closely related structures and overlapping functions. The applicant concluded that any Groucho-interacting protein (GIP) can be use to guide the fate of differentiation of a neuronal progenitor/stem cell, wherein the differentiation is the result of a formation of GIP and Groucho-corepressor protein complex that repress DNA transcription.

However, applicant's arguments are found not persuasive. The instant invention relates to a method of guiding the fate of differentiation of a neuronal progenitor cell into neurons. The scope of invention after recent amendemnt encompasses a method of guiding the fate of differentiation of a neuronal progenitor stem cell into any and all kinds of neurons *(i.e. interneuron, motor neuron, projection neuron, dopaminergic neuron, cortical neuron, gaba-ergic neuron and glutnminergic neuron)* in response to any Groucho-interacting protein (*GIP: which is not limited to Nkx homologs*), which form complex with any Groucho-corepressor protein (*not limited to Grg*). At best the specification teaches that NKx2.2 (a GIP) interacts with Grg4 (a Groucho-corepressor protein) using an in-vitro immunoprecipitation assay (Spec page 74). However, the specification as filed fails to disclose that NKx2.2 is also capable of binding to any other Groucho-

corepressor proteins, especially Grg1, Grg2 or Grg3. Similarly the specification fails to disclose that Grg4 is also capable of binding to the any other Groucho-interacting protein selected from all proteins having a TN-like domain, all proteins having a homeodomain, class I proteins like Pax, Dbx and Irx etc and class II polypeptide including all Nkx-family members especially NKx2.9, Nkx6.2, Nkx6.3, etc. In addition the specification fails to disclose that interaction of all Groucho-interacting proteins with any and all Groucho-corepressor protein is capable of guiding the fate of differentiation neuronal progenitor/stem cells into all kinds of neurons. For example the specification fails to disclose that expression of polypeptide encoded by SEQ ID NO:7, SEQ ID NO:13 and SEQ ID NO:14 would guide the fate of differentiation of any kind of mature cell or a stem cell. Furthermore SEQ ID NO:7 and SEQ ID NO:14 are hypothetical proteins without any biological activity that would guide the fate of differentiation of a cell (any type) to a specific cell type. In addition the specification fails to disclose that contacting the undifferentiated neuronal stem cells in-vivo with NKx2.2 expression vector or NKx2.2 protein is capable of guiding the fate of differentiation to a particular neuronal phenotype like interneuron, motor neuron, projection neuron, dopaminergic neuron, cortical neuron, gaba-ergic neuron or glutnminergic neuron.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). The earlier office action clearly provided the evidence that differentiation of neurons from the neuronal stem cell is complex and relies on the interaction of multiple signaling pathways such as Sonic Hedgehog, Wnts, and BMPs and their antagonists (Placzek et al Nat Rev Neurosci. 3:230-40. 2005, ref of record). Furthermore the role of Sonic Hedgehog signaling during vertebrate development is complex because the differentiation and maintenance of distinct cell types is thought to be controlled by inductive signals acting at different concentration thresholds. The degree of receptor activation in response to these signals is a known determinant of cell fate, but the later steps at which graded signals are converted into all-or-none distinctions in cell identity remain poorly resolved. For example in the ventral neural tube, motor neuron and interneuron generation depends on the graded activity of

the signaling protein Sonic hedgehog (Shh) see Briscoe et al Nature. 398(6728):622-7, 1999, Briscoe et al EMBO, 4(8):761-765, 2003. The instant invention as claimed requires the formation of complex between any Groucho-interacting proteins and any Groucho-corepressor protein, which is considered highly unpredictable in the state of cell differentiation art. The state of the art at the time of filing teaches that Gro/TLE proteins have no intrinsic DNA binding activity but can be targeted to specific gene regulatory regions due to their ability to interact with variety of different DNA-binding transcription factors. It has been postulated that Gro/TLE family proteins probably repress transcription by multiple mechanisms but many aspects of Gro/TLE protein function remain to be explored, including the possible post-translational regulation of Gro/TLE activity as well as the mechanisms by which Gro/TLE proteins direct repression at a distance (Chen et al, Gene 249:1-16, 2000).

Therefore considering the state of the art and limited amount of guidance provided in the instant specification it is highly unpredictable that contacting any cell (undifferentiated or differentiated) with any Groucho-interacting protein would guide the fate of its differentiation to a specific cell type. For example, it would be highly unpredictable that one would be able to guide the fate of differentiation of a neuronal stem cell into any kind of neuron (i.e. insulin producing neuron) by contacting cells with any Nkx gene or gene product. Similarly without any enabling disclosure it is highly unpredictable that any neuronal progenitor/stem cell would differentiate into interneuron, a motor neuron or a Projection neuron selected from a dopaminergic neuron, a cortical neuron, a gaba-ergic neuron and a glutnminergic neuron in response to any GIP. Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S.*

519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case guiding the fate of differentiation of a neuronal progenitor cell (in vivo or ex-vivo) by contacting the cell with any Groucho-interacting protein via any and all means is not considered routine in the art and without sufficient guidance to a specific GIP the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633